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Dated 23 December 2004

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GB 0403254.6

By virtue of a direction given under Section 30 of the Patents Act 1977, the application is proceeding in the name of:

SANDOZ AG,
Lichstrasse 35,
4056 Basel,
Switzerland

[ADP No. 045612700003]

Patents Form 1/77

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1.	Your reference	G-33653P1/ 9951
2.	Patent application number *(The Patent Office will fill in this part)*	0403254.6 13 FEB 2004
3.	Full name, address and postcode of the or of each applicant *(underline all surnames)*	SANDOZ GMBH BIOCHEMIESTRASSE 10 A-6250 KUNDL/TIROL AUSTRIA
	Patent ADP number *(if you know it)*	8638736001
	If the applicant is a corporate body, give the country/state of its incorporation	AUSTRIA
4.	Title of invention	Organic Compounds
5.	Name of your agent *(If you have one)*	Craig McLean
	"Address for service" in the United Kingdom to which all correspondence should be sent *(including the postcode)*	Novartis Pharmaceuticals UK Limited Patents and Trademarks Wimblehurst Road Horsham West Sussex RH12 5AB
	Patents ADP number *(if you know it)*	07181522002

		Country	Priority application number *(if you know it)*	Date of filing (day/month/year)
6.	If you are declaring priority from one ore more earlier patent applications, give the country and the date of filing of the or of each of these earlier applications and *(if you know it)* the or each application number			

		Number of earlier application	Date of filing (day/month/year)
7.	If this application is divided or otherwise derived from an earlier UK application, give the number and the filing date of the earlier application		

8.	Is a statement of inventorship and of right to grant of a patent required in support of this request? *(Answer 'Yes' if:* *a) any applicant named in part 3 is not an inventor, or* *b) there is an inventor who is not named as an applicant, or* *c) any named applicant is a corporate body.* *(see note (d))*	Yes

DUPLICATION 28 (1977 ACT) APPLICATION FILED 12/8/04

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Continuation sheets of this form	
Description	14
Claim(s)	3
Abstract	
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Statement of inventorship and right to grant of a patent *(Patents Form 7/77)*	
Request for preliminary examination and search *(Patents Form 9/77)*	1
Request for substantive examination *(Patents Form 10/77)*	
Any other documents *(please specify)*	

11. I/We request the grant of a patent on the basis of this application

Signature — Date

Craig Mc Lean — 13th February 2004

12. Name and daytime telephone number of person to contact in the United Kingdom

Mr. Trevor Drew — 01403 323069

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G-33653/P1/9950

DUPLICATE

Organic Compounds

This invention relates to a novel compound, to a process for the preparation of such compound, to pharmaceutical compositions containing such compound and to the use of such compound and compositions in medicine.

European Patent Application, Publication Number 0306228 relates to certain thiazolidinedione derivatives disclosed as having hypoglycaemic and hypolipidaemic activity. The compound of example 30 of EP-A-0306228 is 5-[[4-[2-(methyl-2-pyridinylamino) ethoxy]phenyl]methyl]-2,4-thiazolidinedione (according to Merck Index/13th Edition, Monograph number 8346, CAS Registry number: 122320-73-4), i.e. rosiglitazone.

International Application, Publication Number WO 94/05659 discloses certain salts of the compounds of EP-A-0306228. The preferred salt of WO 94/05659 is the maleic acid salt.

There remains a need for alternative salt forms which are straightforward to prepare and which have properties suitable for pharmaceutical processing on a commercial scale.

The present inventors have now prepared and characterised a phosphoric acid salt of 5-[[4-[2-(methyl-2-pyridinylamino)ethoxy]phenyl]methyl]-2,4-thiazolidinedione, hereinafter also referred to as the "Phosphate", and have discovered that the "Phosphate" is particularly stable and hence is suitable for bulk preparation and handling.

The novel Phosphate has also useful pharmaceutical properties and may be used for the treatment and/or prophylaxis of diabetes mellitus, conditions associated with diabetes mellitus and certain complications thereof.

In one aspect therefore, the present invention provides a phosphoric acid salt of 5-[[4-[2-(methyl-2-pyridinylamino)ethoxy]phenyl]methyl]-2,4-thiazolidinedione as a novel compound, preferably as a hydrate.

Phosphoric acid is a triacid, so that the phosphate salts may theoretically exist in more than one stoichiometry. However, the inventors have isolated the Phosphate so far only in the form

in which the ratio of 5-[[4-[2-(methyl-2-pyridinylamino)ethoxy]phenyl]methyl]-2,4-thiazolidinedione to phosphoric acid is or is approximately 1 : 1 (molar ratio), which encompasses molar ratios from 1 : 0.9 to 1 : 1.2. Theoretically, the molar ratio of 5-[[4-[2-(methyl-2-pyridinylamino)ethoxy]phenyl]methyl]-2,4-thiazolidinedione to phosphoric acid could also be 3 : 1 or 2 : 1.

Accordingly, in a further aspect the present invention provides a 5-[[4-[2-(methyl-2-pyridinylamino)ethoxy]phenyl]methyl]-2,4-thiazolidinedione 1 : 1 phosphate as a novel compound, preferably in a hydrated form.

The Phosphate, preferably as a hydrate, may exist in one of several tautomeric forms, all of which are encompassed by the present invention. It will be appreciated that the present invention encompasses all of the isomeric forms of the Phosphate, preferably as a hydrate, including any stereoisomeric forms thereof, whether as individual isomers or as mixtures of isomers.

Without wishing to be bound by any particular mechanism or theory, the present applicants believe that in the 1 : 1 salt the phosphate anion may be associated with a proton (hydrogen atom) in addition to 5-[[4-[2-(methyl-2-pyridinylamino)ethoxy]phenyl]methyl]-2,4-thiazolidinedione, or may be associated with another cation, for example an alkali metal or ammonium cation. In this case, the salt may be described as a mixed salt.

As indicated above, the preferred aspect of the invention is a hydrate of the Phosphate which hereinafter is also referred to as “Phosphate Hydrate”.

The Phosphate in which the ratio of 5-[[4-[2-(methyl-2-pyridinylamino)ethoxy]phenyl] methyl]-2,4-thiazolidinedione to phosphoric acid is (by mole) 1 : 1 has been isolated as a Phosphate Hydrate containing approximately 0.1% - 4.5%, e.g. approximately 0.8 % - 4 %, e.g. preferably 1.6% - 3.6% by weight water.

The present invention also encompasses the Phosphate containing less than 0.1 % by weight water, i.e. the anhydrous Phosphate.

A particular example of a Phosphate Hydrate contains approximately 0.87% of water, consistent with a 1 : 0.23 hydrate. Further particular examples contain approximately 1.6% of water, consistent with a 1 : 0.42 hydrate, or approximately 2.3 % of water, consistent with a

1 : 0.60 hydrate, or 3.3% of water, consistent with a 1 : 0.79 hydrate, or 3.58% of water, consistent with a 1 : 0.94 hydrate. All percentages are by weight.

Drying of the Phosphate Hydrate under normal conditions e.g. drying at ambient temperatures results in an approximately 1 : 0.4 hydrate; drying with the aid of a strong desiccant, e.g. P_2O_5, at about 45°C results in an approximately 1: 0.3 hydrate, and optional further drying at elevated temperatures, e.g. 70°C – 100°C, preferably 80°C, may lead to a water content of less than 0.1% by weight.

Exposure of the Phosphate Hydrate to high humidity results in an approximately 1 : 1 hydrate.

Accordingly, in a further aspect the present invention provides 5-[[4-[2-(methyl-2-pyridinylamino)ethoxy]phenyl]methyl]-2,4-thiazolidinedione phosphate (molar ratio 1 : 1) as a novel compound containing approximately up to 4.5% by weight water.

Alternatively, the present invention provides 5-[[4-[2-(methyl-2-pyridinylamino)ethoxy] phenyl]methyl]-2,4-thiazolidinedione phosphate (molar ratio 1 : 1) which is a hydrate or which is anhydrous, i.e. contains less than 0.1% water by weight.

In another aspect the present invention comprises a 5-[[4-[2-(methyl-2-pyridinylamino)ethoxy] phenyl]methyl]-2,4-thiazolidinedione phosphate (molar ratio 1 : 1) which contains approximately 1.6% water by weight being consistent to a 1 : 0.42 hydrate.

In an additional aspect the present invention provides 5-[[4-[2-(methyl-2-pyridinylamino)ethoxy] phenyl]methyl]-2,4-thiazolidinedione phosphate (molar ratio 1 : 1) which contains approximately 3.6% water by weight being consistent to a 1 : 0.94 hydrate.

However , since the water content cannot be fixed to exactly to a molar ratio as mentioned above, in one suitable embodiment, there is provided a Phosphate Hydrate characterised by :

i) an infrared spectrum substantially in accordance with Figure 1, and / or
ii) an X-ray powder diffraction (XRPD) pattern substantially in accordance with Table 1 and Figure 2.

Figure 1 shows the infrared spectrum of the Phosphate Hydrate wherein the scale of the abscissa is the wave number in cm^{-1} , and the ordinate is transmittance in %.

Figure 2 shows the X-ray powder diffraction (XRPD) pattern of the Phosphate Hydrate, wherein the scale of the abscissa is in degrees 2θ, and the ordinate is the linear intensity in counts per second (cps)

Table 1 shows the interplanar spacings (**d**, given in **Å**, i.e. Angstroem), characteristic XRPD angles (**2 theta°**) and **relative intensities** (in **%**).

In one favoured aspect, the Phosphate Hydrate provides an infrared spectrum substantially in accordance with Figure 1.

In another favoured aspect, the Phosphate Hydrate provides a X-Ray powder diffraction (XRPD) pattern substantially in accordance with Table 1 and Figure 2.

In a preferred aspect, the invention provides a 5-[[4-[2-(methyl-2-pyridinylamino)ethoxy] phenyl]methyl]-2,4-thiazolidinedione phosphate hydrate characterised by:

i) an infrared spectrum substantially in accordance with Figure 1, and

ii) an X-ray powder diffraction (XRPD) pattern substantially in accordance with Table 1 and Figure 2.

Depending on the solvent from which the Phosphate is recovered, the Phosphate may be obtained as a solvate other than a hydrate. Such solvates form part of the present invention. References to the Phosphate hereinafter include solvates thereof.

The present invention encompasses the Phosphate, preferably as the Phosphate Hydrate, when isolated in pure form or when admixed with other materials, e.g. pharmaceutically acceptable carriers.

Thus in one aspect there is provided the Phosphate, preferably as the Phosphate Hydrate, in isolated form.

In a further aspect there is provided the Phosphate, preferably as the Phosphate Hydrate, in substantially pure form.

In yet a further aspect there is provided the Phosphate, preferably as the Phosphate Hydrate, in crystalline form.

In an alternative aspect there is provided the Phosphate, preferably as the Phosphate Hydrate, in non-crystalline form.

In a further aspect, the present invention also provides the Phosphate, preferably as the Phosphate Hydrate, in a pharmaceutically acceptable form, especially in bulk form, such form being capable of being further processed, e.g. milled, according to known processes. The invention further provides the Phosphate, preferably as the Phosphate Hydrate, in a pharmaceutically acceptable form, e.g. in a milled form.

In another aspect, the invention provides a process for preparing the Phosphate, preferably the Phosphate Hydrate, comprising reacting 5-[[4-[2-(methyl-2-pyridinylamino)ethoxy]phenyl] methyl]-2,4-thiazolidinedione or a salt thereof, preferably dispersed or suspended or dissolved in a suitable solvent medium, with a suitable source of a phosphate ion, e.g. phosphoric acid, and thereafter, if required, carrying out one or more of the following optional steps:

i) forming a solvate thereof;

ii) recovering the Phosphate, preferably the Phosphate Hydrate;

iii) drying the product obtained, especially under vacuum.

Optionally, the Phosphate, preferably the Phosphate Hydrate, may be further processed in known manufacturing processes, e.g. in a milling process.

Alternatively, 5-[[4-[2-(methyl-2-pyridinylamino)ethoxy] phenyl] methyl]-2,4-thiazolidinedione or a salt thereof, may be added as a powder to the suitable source of the phosphate ion.

In general Phosphates may be prepared by contacting stoichiometric amounts, for example 1 : 1, of phosphoric acid and 5-[[4-[2-(methyl-2-pyridinylamino)ethoxy]phenyl]methyl]-2,4-thiazolidinedione, or alternatively using an excess of phosphoric acid, e.g. a ratio of 2 : 1 to 2.5 : 1 of phosphoric acid and 5-[[4-[2-(methyl-2-pyridinylamino)ethoxy]phenyl] methyl]-2,4-thiazolidinedione.

The concentration of 5-[[4-[2-(methyl-2-pyridinylamino)ethoxy]phenyl]methyl]-2,4-thiazolidinedione is preferably in the range of 1 to 50% weight/volume, more preferably 1 – 10% weight/volume related to the total amount of solvent medium used in the reaction.

A suitable solvent medium for the solution or dispersion or suspension of 5-[[4-[2-(methyl-2-pyridinylamino)ethoxy]phenyl]methyl]-2,4-thiazolidinedione or a salt thereof, and the reaction with a suitable source of the phosphate ion, as described above, is an organic solvent medium, e.g. a ketone, e.g. acetone, or an alcohol, e.g. a $C_1 - C_4$ alcohol, e.g. ethanol, or a nitrile, e.g. acetonitrile, or an ether, e.g. tetrahydrofuran, or mixtures thereof, or water, or mixtures of said organic solvent media with water.

Preferably, water is used as a cosolvens. Preferred amounts of water are 1 to 100% (v/v), preferably 1 to 20 % (v/v) of water related to the organic solvent medium.

A suitable source of the phosphate ion is phosphoric acid, for example 85% (w/w) phosphoric acid or less concentrated phosphoric acid, e.g. diluted from 1 : 1 to 1 : 10 w/v with water or with an organic solvent medium such as a ketone, e.g. acetone, or an alcohol, e.g. a $C_1 - C_4$ alcohol, e.g. ethanol, or mixtures of a ketone and an alcohol. The phosphoric acid is preferably added as such, or as a solution, for example a solution in one of the above mentioned organic solvent media.

An alternative source of the phosphate ion may be metaphosphoric acid, preferably in combination with water, or sodium or potassium dihydrogenphosphate, disodium or dipotassium hydrogenphosphate or trisodium or tripotassium phosphate in combination with a mineral acid, preferably phosphoric acid.

Formation of the Phosphate Hydrate requires the presence of water at some stage. The water may be present in the source of the phosphate ion, e.g. in the phosphoric acid used, e.g. by using 85% (w/w) or less concentrated phosphoric acid, or the water may be present as a cosolvens in the process, e.g. 1 to 100% (v/v), preferably 1 – 20%, of water related to the organic solvent medium.
However, it is also possible to provide sufficient water for the formation of the Phosphate Hydrate by carrying out the reaction with exposure to atmospheric moisture, or by the use of a non-anhydrous solvent medium, e.g. aqueous acetone, or of a non-anhydrous source of the phosphate ion, e.g. 85% (w/w) phosphoric acid.

The reaction may be carried out at ambient temperature, e.g. at approximately 20 – 35°C, or at elevated temperatures of e.g. 35 to 60°C, preferably at 30 to 50°C, or at the reflux temperature

of the solvent medium, although any convenient temperature that provides the required product may be employed.

Solvates, preferably the hydrates, of the Phosphate are to be prepared, e.g. by crystallising from a solvent medium as described above which may provide or contain the solvate moiety, or by exposing the Phosphate to the solvate moiety as a vapour.

Recovery of the required compound, e.g. the Phosphate, preferably the Phosphate Hydrate, before drying comprises isolation from an appropriate solvent medium, which is optionally the above mentioned solvent medium used for the above described reaction, preferably with water as a cosolvens, or which is a mixture of said solvent media, or alternatively a different solvent medium or mixture thereof, e.g. a $C_1 - C_4$ alkyl acetate, or e.g. a hydrogenated carbon, e.g. hexane.

Alternatively the required compound may be isolated by crystallisation from the appropriate solvent medium or mixture of solvent media as described above which may be initiated by the use of seed crystals. Careful control of precipitation temperature from approximately 20 – 30°C to about 0 – 20°C, and/or the use of seed crystals are useful to improve the reproducibility of the Phosphate, preferably the Phosphate Hydrate.

Optionally, the required compound, e.g. the Phosphate, preferably the Phosphate Hydrate, may be further processed without being isolated from the mixture of the reaction as described above.

Preferably the isolated Phosphate Hydrate is dried under vacuum at ambient temperature, e.g. 20 – 35°C or at elevated temperatures, e.g. 35 – 80°C. The drying is optionally carried out over a desiccant, e.g. phosphorus pentoxide. Drying is continued until the water content is below approximately 4.5%, e.g. 3.58%, e.g. less than 0.1% by weight.

5-[[4-[2-(methyl-2-pyridinylamino)ethoxy]phenyl]methyl]-2,4-thiazolidinedione may be prepared according to known procedures, such as the method disclosed in EP-A-0306228.

As mentioned above the compound of the invention has useful therapeutic properties. The present invention accordingly provides a Phosphate, preferably as the Phosphate Hydrate, for use as an active therapeutic substance.

Particularly, the present invention provides the Phosphate, preferably the Phosphate Hydrate, for use in the treatment and/or prophylaxis hyperglycaemia.
More particularly, the present invention provides the Phosphate, preferably the Phosphate Hydrate, for use in the treatment of diabetes mellitus, conditions associated with diabetes mellitus and certain complications thereof.

When used herein, the term "prophylaxis of conditions associated with diabetes mellitus" includes treating conditions such as insulin resistance, impaired glucose tolerance, hyperinsulinaemia and gestational diabetes. Diabetes mellitus preferably means Type II diabetes mellitus.
Conditions associated with diabetes mellitus include hyperglycaemia, hyperlipidaemia, obesity, hypertension, cardiovascular disease, certain eating disorders, polycystic ovarian syndrome and steroid induced insulin resistance.
Complications of conditions associated with diabetes mellitus encompassed herein include renal disease, especially renal disease associated with the development of Type II diabetes mellitus including diabetic nephropathy, glomerulonephritis, glomerular sclerosis, nephrotic syndrome, hypertensive nephrosclerosis and end stage renal disease.

The Phosphate, preferably the Phosphate Hydrate, may be administered per se, or preferably, as a pharmaceutical composition also comprising a pharmaceutically acceptable carrier.

Accordingly, the present invention also provides a pharmaceutical composition comprising the Phosphate, preferably the Phosphate Hydrate, and a pharmaceutically acceptable carrier thereof.
As used herein, the term "pharmaceutically acceptable" embraces compounds, compositions and ingredients for both human and veterinary use.
In accordance with conventional pharmaceutical practice the carrier may comprise a diluent, filler, disintegrant, wetting agent, lubricant, colourant, flavourant or other conventional adjuvant.

The compound of the present invention may be administered by any suitable route, but usually by the oral or parenteral routes.

Pharmaceutical compositions are prepared by admixture and are suitably adapted for oral, parenteral or topical administration, and as such may be in the form of tablets, capsules, oral liquid preparations, powders, granules, lozenges, pastilles, reconstitutable powders, injectable and infusable solutions or suspensions, suppositories and transdermal devices.

Suitable methods for formulating the pharmaceutical compositions of the Phosphate, preferably the Phosphate Hydrate, are known.

The present invention further provides a method for the treatment and/or prophylaxis of diabetes mellitus, conditions associated with diabetes mellitus and certain complications thereof, in a human or non-human mammal which comprises administering an effective, non-toxic, amount of the Phosphate, preferably the Phosphate Hydrate, to a human or non-human mammal in need thereof.

In the treatment and/or prophylaxis of diabetes mellitus, conditions associated with diabetes mellitus and certain complications thereof, the Phosphate, preferably the Phosphate Hydrate, may be taken in amounts so as to provide 5-[[4-[2-(methyl-2-pyridinylamino)ethoxy]phenyl] methyl]-2,4-thiazolidinedione in suitable doses, e.g. such as disclosed in EP-A-0306228.

In a further aspect, the present invention provides the use of the Phosphate, preferably the Phosphate Hydrate, for the manufacture of a medicament for the treatment and/or prophylaxis of diabetes mellitus, conditions associated with diabetes mellitus and certain complications thereof.

Additionally, the present invention provides the use of the Phosphate, preferably the Phosphate Hydrate, in combination with one or more other anti-diabetic agents, e.g . biguanidines, sulfonylureas and alpha glucosidase inhibitors, for the manufacture of a medicament for the treatment and/or prophylaxis of diabetes mellitus, conditions associated with diabetes mellitus and certain complications thereof.

The following examples illustrate the invention but do not limit it in any way. All temperatures are given in degree Celsius and are uncorrected. The water content is determined by the Karl Fisher method.

Example 1:

Preparation of 5-[[4-[2-(methyl-2-pyridinylamino)ethoxy]phenyl]methyl]-2,4-thiazolidinedione phosphate hydrate

5 g of 5-[[4-[2-(methyl-2-pyridinylamino)ethoxy]phenyl]methyl]-2,4-thiazolidinedione are dissolved in a mixture of 250 ml acetone and 20 ml of H_2O at approximately 30°C. The solution is stirred and 1.89 ml of 85% phosphoric acid are added with stirring. Seed crystals of the title compound are added, stirring is stopped and the suspension is allowed to stand at ambient temperature for about 3 hours with stirring for 2 to 3 minutes in 30 minute intervals. The title compound is isolated by suction, washed with 25 ml of acetone and dried in vacuo for approximately 15 hours at ambient temperature, and obtained as white crystalline solid.
Yield (5-[[4-[2-(methyl-2-pyridinylamino)ethoxy]phenyl]methyl]-2,4-thiazolidinedione phosphate hydrate): 5.54 g
Water content (Karl Fisher): 1.6 % w/w
Content Phosphoric acid: 21.7% (by ion chromatography)

Example 2:

Preparation of 5-[[4-[2-(methyl-2-pyridinylamino)ethoxy]phenyl]methyl]-2,4-thiazolidinedione phosphate hydrate

25 g of 5-[[4-[2-(methyl-2-pyridinylamino)ethoxy]phenyl]methyl]-2,4-thiazolidinedione are dissolved in a mixture of 1250 ml of acetone and 100 ml of H_2O at approximately 30°C. The solution is stirred, and 9.45 ml of 85% phosphoric acid are added with stirring. Stirring is stopped, and the suspension is allowed to stand at ambient temperature for about 18 hours . The suspension is then gently stirred for about 1 hour. The white crystals are then isolated by suction, washed with a mixture of 95 ml of acetone and 5 ml H_2O and dried in vacuo for approximately 3 hours at ambient temperature.
Yield (5-[[4-[2-(methyl-2-pyridinylamino)ethoxy]phenyl]methyl]-2,4-thiazolidinedione phosphate hydrate): 28.56 g
Water content (Karl Fisher): 3.3 % w/w

Characterising data for the product of Example 2:

Infrared absorption spectrum

The infrared spectrum of the solid product as obtained by Example 2 **(Figure 1)** was recorded using a BRUKER FTIR-Tensor 27. Bands were observed at 2704 (broad), 1748, 1701 (broad), 1643, 1611, 1546, 1513, 1469, 1420, 1391, 1330, 1302, 1244, 1110, 1028, 928, 821, 767, 716 cm^{-1}.

X-Ray Powder Diffraction (XRPD) pattern

The X-Ray Powder Diffraction (XRPD) pattern of the solid product as obtained by Example 2 is shown in **Figure 2** (scale of the abscissa in degrees 2θ, and the ordinate is the linear intensity in counts per second, i.e. cps) and was recorded under the following conditions:
Equipment: X-Ray Powder Diffractometer D-8 (AXS-BRUKER), theta-theta-goniometer, sample changer, target: Copper, Kα1+Kα2 λ = 1.5406 Å, parallel beam optics (receiving soller-slit: 0.07 mm), Scintillation counter, standard sample holders.
Data collection: Tube anode: Cu; Generator tension: 40kV; Generator current: 40mA; Start angle: 2.0° 2θ, End angle: 40.0° 2θ; Step size: 0.01° 2θ; Time per step: 2 seconds; 2θ may vary 1 to 3% absolutely.
Interplanar spacings (**d**, given in **Å**, i.e. Angstroem), characteristic XRPD angles (**2 theta°**) and **relative intensities** (in **%**) are recorded in **Table 1**.

Table 1

d-value (Å)	Angle 2 theta°	Rel.Intensity (%)
22.66	3.90	13
20.63	4.28	21
16.42	5.38	18
14.20	6.22	7
10.51	8.41	16
10.26	8.61	19
9.879	8.94	7
8.911	9.92	18
8.170	10.82	6
7.514	11.77	7
7.111	12.44	24
6.828	12.96	10
6.748	13.11	9
6.497	13.62	13
6.301	14.04	31

(continued)

d-value (Å)	Angle 2 theta°	Rel.Intensity (%)
5.667	15.63	65
5.622	15.75	100
5.514	16.06	16
5.239	16.91	19
5.123	17.30	42
4.924	18.00	17
4.855	18.26	9
4.663	19.02	15
4.524	19.61	35
4.342	20.44	14
4.135	21.47	40
4.100	21.66	33
4.037	22.00	16
3.941	22.54	30
3.876	22.93	12
3.817	23.29	13
3.803	23.37	15
3.777	23.54	16
3.741	23.77	15
3.690	24.10	18
3.641	24.43	18
3.591	24.77	18
3.550	25.06	18
3.449	25.81	19
3.389	26.28	23
3.279	27.17	8
3.227	27.62	14
3.201	27.85	14
3.128	28.51	9
3.066	29.11	10
3.025	29.51	14
2.957	30.20	9
2.922	30.57	12
2.910	30.70	13
2.829	31.60	10
2.807	31.86	9
2.774	32.25	9
2.759	32.42	9
2.711	33.01	7
2.674	33.49	7
2.617	34.24	10
2.608	34.36	11
2.568	34.91	8
2.556	35.08	8
2.452	36.61	7

(continued)

d-value (Å)	Angle 2 theta°	Rel.Intensity (%)
2.421	37.11	7
2.367	37.98	6
2.330	38.60	7
2.302	39.10	8
2.273	39.62	8

Example 3 :

Preparation of 5-[[4-[2-(methyl-2-pyridinylamino)ethoxy]phenyl]methyl]-2,4-thiazolidinedione phosphate hydrate

10 g of 5-[[4-[2-(methyl-2-pyridinylamino)ethoxy]phenyl]methyl]-2,4-thiazolidinedione are dissolved in a mixture of 500 ml 96% ethanol and 50 ml of H_2O at approximately 60°C. 2.1 ml of 85% phosphoric acid are added. With stirring seed crystals of 5-[[4-[2-(methyl-2-pyridinylamino)ethoxy]phenyl]methyl]-2,4-thiazolidinedione phosphate are added, and the stirring is stopped. The suspension is allowed to stand at ambient temperature for about 3 hours with stirring for 2 to 3 minutes in 30 minute intervals. The title compound is isolated by suction, washed in 2 portions with a total of 50 ml of ethanol and dried at ambient temperature in vacuo for about 4 days, and obtained as white crystalline solid.

Yield (5-[[4-[2-(methyl-2-pyridinylamino)ethoxy]phenyl]methyl]-2,4-thiazolidinedione phosphate hydrate): 10.32 g

Water content (Karl Fisher): 2.3 % w/w

Content Phosphoric acid: 20.1% (by ion chromatography)

Example 4 :

Drying of 5-[[4-[2-(methyl-2-pyridinylamino)ethoxy]phenyl]methyl]-2,4-thiazolidinedione phosphate hydrate with phosphorus pentoxide

10 g of 5-[[4-[2-(methyl-2-pyridinylamino)ethoxy]phenyl]methyl]-2,4-thiazolidinedione phosphate hydrate, water content (Karl Fisher) 2.8% w/w, are dried at a temperature of about 45°C for about 24 hours in vacuo in presence of P_2O_5 .

Water content (Karl Fisher): 0.87% w/w

Example 5 :

Exposure of 5-[[4-[2-(methyl-2-pyridinylamino)ethoxy]phenyl]methyl]-2,4-thiazolidinedione phosphate hydrate to humidity

5-[[4-[2-(methyl-2-pyridinylamino)ethoxy]phenyl]methyl]-2,4-thiazolidinedione phosphate hydrate was exposed to different relative humidities for about 24 hours. Results are given below in **Table 2** :

Table 2

	Water content (Karl Fisher) (%) w/w
Initial	2.8
45% relative humidity	3.42
63% relative humidity	3.37
86% relative humidity	3.58

The Phosphate, preferably the Phosphate Hydrate, as herein described, shows high stability. After a stress test according to known methods, which was performed at 80°C for about 160 hours in a closed vial, no degradation has been observed as determined by HPLC using standard methods.

Furthermore, the present applicants have observed that the 5-[[4-[2-(methyl-2-pyridinylamino)ethoxy]phenyl]methyl]-2,4-thiazolidinedione phosphate, preferably the hydrate thereof, according to the present invention, exhibits a more expressed solubility in water when compared to rosiglitazone maleate which is the main form in which rosiglitazone is currently marketed as active substance in pharmaceutical preparations. This enhanced solubility in water, being e.g. about twice as high as that of the maleate form, is useful and interesting for industrial application.

Additionally, the process for the production of the Phosphate, preferably the Phosphate Hydrate, is relatively simple.

Claims:

1. A salt of 5-[[4-[2-(methyl-2-pyridinylamino)ethoxy]phenyl]methyl]-2,4-thiazolidinedione and phosphoric acid, or a solvate thereof.

2. A salt as claimed in claim 1, being 5-[[4-[2-(methyl-2-pyridinylamino)ethoxy]phenyl] methyl]-2,4-thiazolidinedione phosphate (molar ratio 1 : 1), or a solvate thereof.

3. A salt as claimed in claim 1, being 5-[[4-[2-(methyl-2-pyridinylamino)ethoxy]phenyl] methyl]-2,4-thiazolidinedione (1 : 1) phosphate containing up to approximately 4.5 % water by weight.

4. A salt as claimed in claim 1, being 5-[[4-[2-(methyl-2-pyridinylamino)ethoxy]phenyl] methyl]-2,4-thiazolidinedione (1 : 1) phosphate hydrate containing approximately 0.1% to 4.5 % water by weight.

5. A salt as claimed in claim 1, being 5-[[4-[2-(methyl-2-pyridinylamino)ethoxy]phenyl] methyl]-2,4-thiazolidinedione (1 : 1) phosphate hydrate containing approximately 1.5% to 4% water by weight.

6. A salt as claimed in claim 1, being 5-[[4-[2-(methyl-2-pyridinylamino)ethoxy]phenyl] methyl]-2,4-thiazolidinedione (1 : 1) phosphate hydrate, characterised by
   i) an infrared spectrum substantially in accordance with Figure 1; and/or
   ii) an X-ray powder diffraction (XRPD) pattern substantially in accordance with Table 1 and Figure 2

7. A salt as claimed in claim 1, being 5-[[4-[2-(methyl-2-pyridinylamino)ethoxy]phenyl] methyl]-2,4-thiazolidinedione (1 : 1) phosphate hydrate, characterised by an infrared spectrum substantially in accordance with Figure 1

8. A salt as claimed in claim 1, being 5-[[4-[2-(methyl-2-pyridinylamino)ethoxy]phenyl] methyl]-2,4-thiazolidinedione (1 : 1) phosphate hydrate, characterised by an X-ray powder diffraction (XRPD) pattern substantially in accordance with Table 1 and Figure 2

9. A salt as claimed in claim 1, being 5-[[4-[2-(methyl-2-pyridinylamino)ethoxy]phenyl] methyl]-2,4-thiazolidinedione (1 : 1) phosphate hydrate, characterised by

i) an infrared spectrum substantially in accordance with Figure 1, and

ii) an X-ray powder diffraction (XRPD) pattern substantially in accordance with Table 1 and Figure 2

10. A compound as claimed in any of claims 1 to 9 in crystalline form

11. A compound as claimed in any of claims 1 to 9 in isolated form

12. A compound as claimed in any of claims 1 to 9 in substantially pure form

13. A compound as claimed in any of claims 1 to 9 in non-crystalline form

14. A process for preparing a compound as claimed in any of claims 1 to 9, comprising reacting 5-[[4-[2-(methyl-2-pyridinylamino)ethoxy]phenyl] methyl]-2,4-thiazolidinedione or a salt thereof, preferably dispersed or suspended or dissolved in a suitable solvent medium, with a suitable source of a phosphate ion, e.g. phosphoric acid, and thereafter, if required, carrying out one or more of the following optional steps:

i) forming a solvate thereof,

ii) recovering the Phosphate, preferably the Phosphate Hydrate,

iii) drying the product obtained, especially under vacuum,

iv) further processing the Phosphate, preferably the Phosphate Hydrate.

15. A process as claimed in claim 14, wherein the suitable source of the phosphate ion is phosphoric acid.

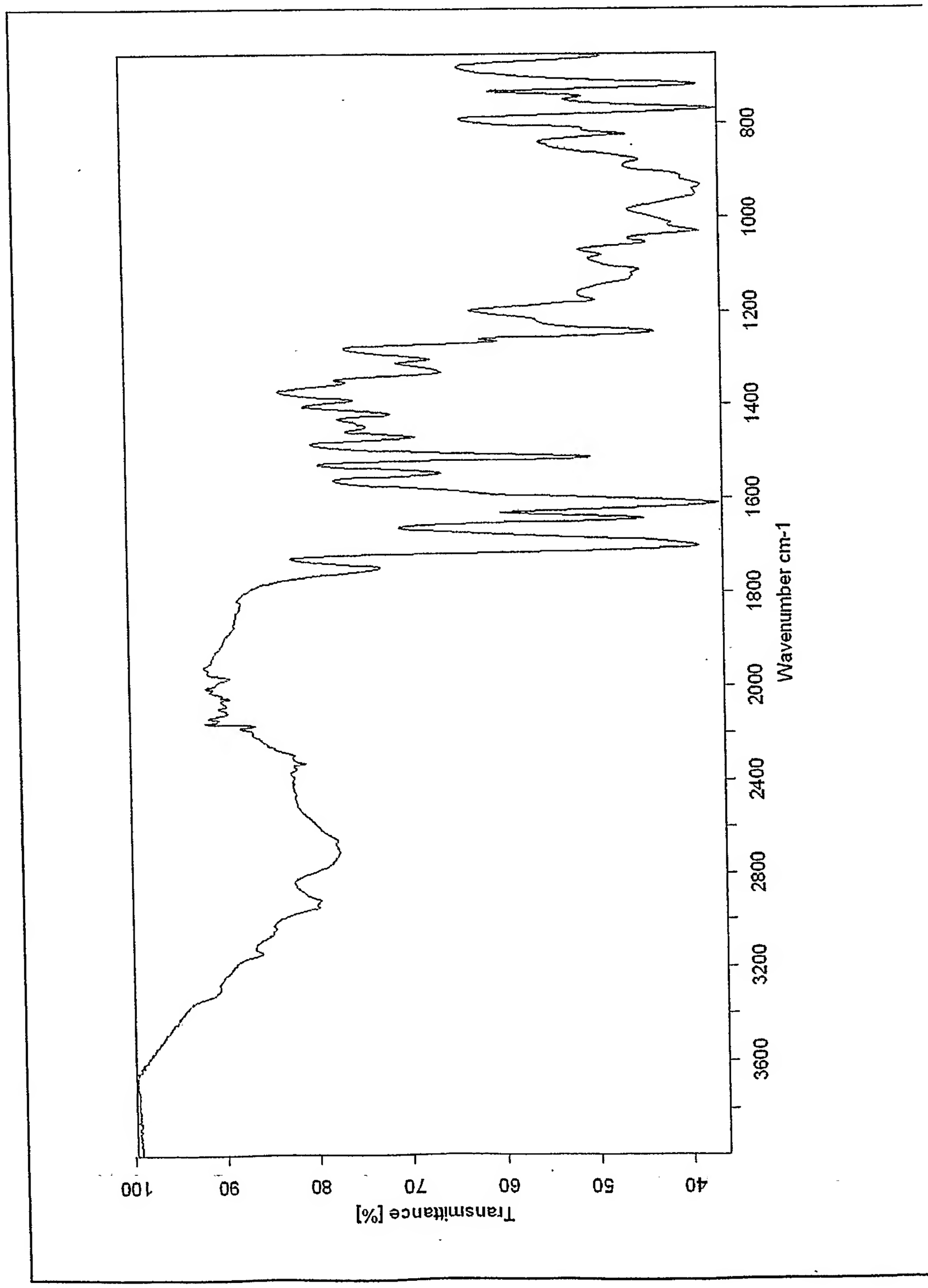
16. A pharmaceutical composition comprising a compound as claimed in any of claims 1 to 13, and a pharmaceutically acceptable carrier therefor.

17. A pharmaceutical composition comprising a compound as claimed in any of claims 1 to 13, in combination with one or more other anti-diabetic agents, and optionally a pharmaceutically acceptable carrier therefor.

18. A compound as claimed in any of claims 1 to 13, for use as an active therapeutic substance.

19. The use of a compound as claimed in claim 1 to 13, for the manufacture of a medicament for the treatment and/or prophylaxis of diabetes mellitus, conditions associated with diabetes mellitus and certain complications thereof.

Figure 1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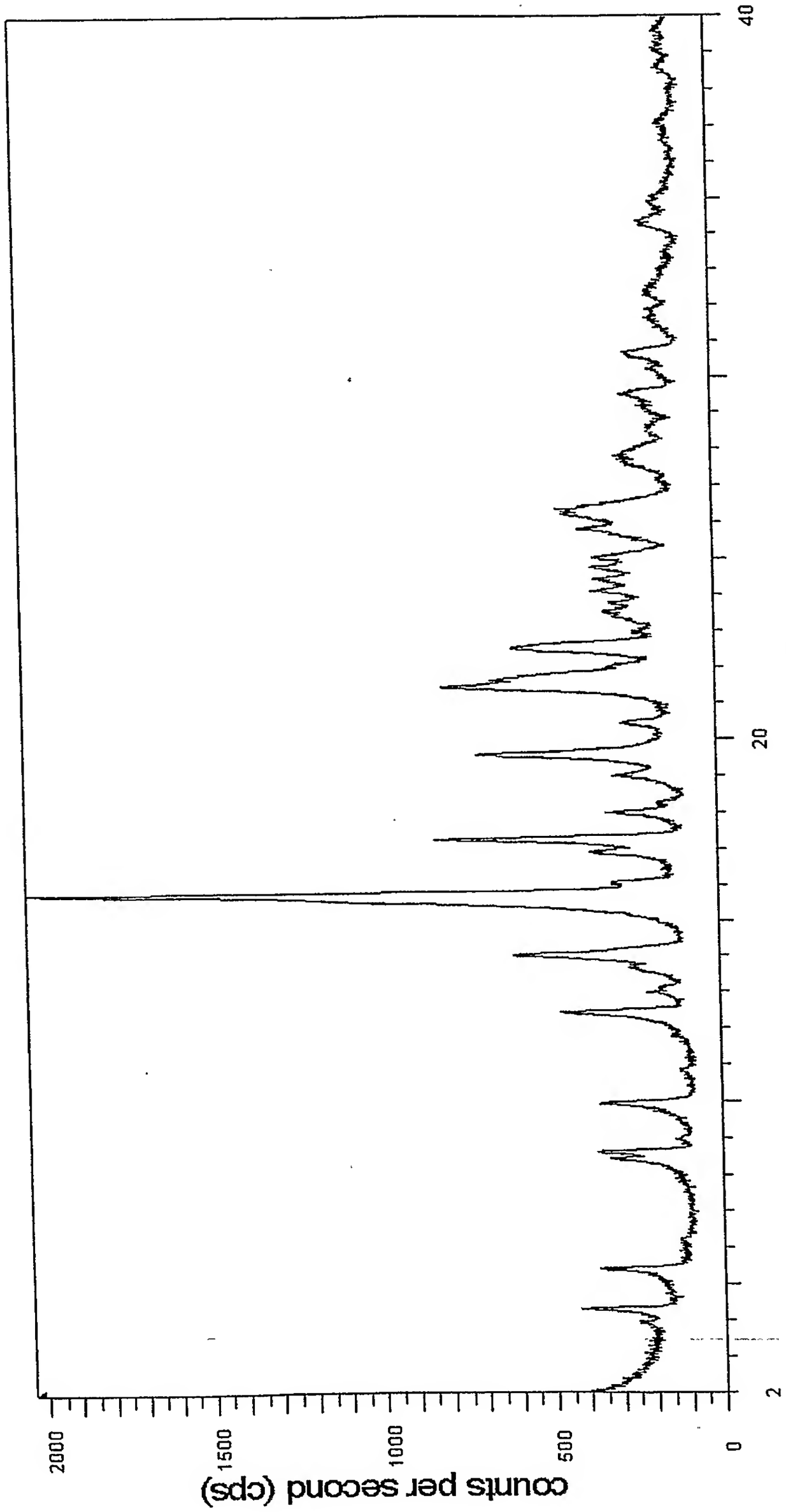
80
70
60
50
40
3600
3200
2800
2400
2000
1800
1600
1400
1200
1000
800
Wavenumber cm-1

Figure 2


counts per second (cps)
2000
1500
1000
500
0
2
20
40
2-Theta - Scale